

**REMARKS**

Reconsideration of the present application is requested based on the foregoing amendments and the following remarks.

**I. Claim Amendments**

Claims 1-35 are pending in the present application.

Claims 1 and 17 are currently amended. It is acknowledged that the foregoing amendments are submitted after final rejection of the claims. However, because the amendments do not introduce new matter, and either place the application in condition for allowance or at least in better condition for appeal, entry thereof by the Examiner is respectfully requested.

In particular, claims 1 and 17 have been amended to incorporate limitations that are substantially similar to the limitations of claims 9 and 10, and claim 17 has been amended to incorporate limitations that are substantially similar to the limitations of claims 25 and 26. In addition, claims 1 and 17 have been amended to recite "at a time not more than 12 days from culturing." Support for these amendments can be found in the specification, in particular at Example 2, paragraph [0059] which recites:

Discs of engineered cartilage tissue was punched out from engineered cartilage tissue on *day 7 and cultured for 5 days* in complete medium with/without IL-1 $\alpha$  (1 ng/ml). Engineered cartilage tissue was obtained as described above. *On days 1, 2, 3 and 5*, the discs were harvested and digested with papain. After digestion the contents of sulfated PG and DNA were measured by the DMMB method and Hoechst 33258-dye method, respectively.

As such, the Applicants respectfully submit that the specification provides support for the limitation "at a time not more than 12 days."

Claims 9, 10, 25, and 26 are requested to be cancelled without disclaimer or prejudice to further prosecution on the merits.

After entry of the amendments, claims 1-8, 11-24, and 27-35 are pending. Claims 15, 16, 31 and 32 have been withdrawn from consideration.

**II. Claim Rejections – 35 U.S.C. § 112**

Claims 1-14, 17-30 and 33-35 were rejected under 35 U.S.C. § 112, first or second paragraph, for reciting the phrase “but short enough such that the collagen fibrils in the cell associated matrix do not become overly crosslinked.” As amended, the claims do not recite this phrase. Withdrawal of the rejections are requested.

**III. Claim Rejections – 35 U.S.C. § 103**

The claims stand rejected under 35 U.S.C. § 103 over cited references that include Kai *et al.*, Purchio *et al.*, Saito *et al.*, Huch *et al.*, and Lansbury *et al.* in view of U.S. Patent No. 6,197,061 (“the Masuda ‘061 Patent”) as set forth in previously issued Office Actions. Reconsideration and withdrawal of the rejections are requested in view of the foregoing claim amendments and for the following reasons.

First, the claims have been amended to recite:

“measuring proteoglycan loss from the engineered cartilage tissue at a time not more than 12 days from culturing, without use of a radioactive agent, to determine whether the test agent has an effect on the contacted cells or tissue.”

This is an affirmative limitation of the claims which is not taught or suggested in the cited prior art references, either alone or in combination. Therefore, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are requested in view of the claim amendments.

With respect to “culture time,” the claims recite “at a time not more than 12 days from culturing.” It is respectfully noted that rapid degradation and reduction of proteoglycan content is inversely correlated to “culture time.” In other words, if a tissue is cultured for too long, it may not exhibit rapid degradation and reduction of proteoglycan content, and therefore, may not be suitable for the claimed methods. It also respectfully is noted that “rapid degradation and reduction of proteoglycan content” is not a universal trait of all the engineered cartilage tissues taught by the Masuda ‘061 Patent. Some of the tissues taught by the Masuda ‘061 Patent may be matured to a point (*i.e.*, cultured for too long a period) where the tissue would not be suitable for the claimed methods because proteoglycan degradation would take several days after treatment with IL-1. Therefore, one of skill in the art would have to rely on the Applicants’ present disclosure in order to select engineered cartilage tissues, as disclosed by the Masuda ‘061 Patent, which would be suitable for the claimed methods. None of the cited references, including the Masuda ‘061 Patent, teach or suggest use of the selected engineered cartilage tissue as recited in the present claims for performing the claimed methods.

With respect to “inherency,” the Office Action states that “the discovery of a previously unappreciated property of a prior art composition...does not render the old **composition** patentably new to the discoverer” (emphasis added). However, it respectfully is noted that the present claims recite methods not compositions. In the methods, a previously unappreciated trait in selected samples of engineered cartilage tissues is exploited. The fact that the trait may have been inherent and previously unappreciated does not render the claimed methods unpatentable. In fact, there are enumerable examples in U.S. patent law of patentable methods that exploit a previously unappreciated trait of a known material. Whether the exploited trait is inherent is irrelevant to the present claims because the claims recite methods that include affirmative steps which are not taught or suggested in the cited prior art references (*e.g.*, “measuring proteoglycan loss from the engineered cartilage tissue at a time not more than 12 days from culturing, without use of a radioactive agent”). Furthermore, the trait exploited in the recited methods is not inherent to all the tissues disclosed in the Masuda ‘061 Patent. One of skill in the art would have to rely on the Applicants’ present specification in order to select engineered cartilage tissues, as disclosed

by the Masuda '061 Patent, which would be suitable for the claimed methods. As such, the claimed methods are patentable over the cited references.

If the present rejections under 35 U.S.C. § 103 continue to be maintained in an Advisory Action, the Applicants respectfully request that the Examiner point out where the cited references teach or suggest, either alone or in combination, a method that includes the following step:

“measuring proteoglycan loss from the engineered cartilage tissue at a time not more than 12 days from culturing, without use of a radioactive agent, to determine whether the test agent has an effect on the contacted cells or tissue.”

For all these reasons, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are requested.

**IV. Kai et al. in view of the Masuda '061 Patent**

Claims 1-8, 10, 14, 17-24, 26, 29-30 and 33 stand “rejected under 35 U.S.C. 103(a) as being unpatentable over Kai *et al.* (JP 2001 089390 A) in view of the Masuda '061 Patent. The Applicants traverse the rejection because the combination of Kai *et al.* and the Masuda '061 Patent do not teach or suggest all the limitations of the claims as amended. In particular, the combination of Kai *et al.* and the Masuda '061 Patent do not teach or suggest “measuring proteoglycan loss from the engineered cartilage tissue at a time not more than 12 days from culturing, without use of a radioactive agent.”

Kai *et al.* discloses a “method of screening [a] therapeutic agent for [ ] cartilage disorders [which includes] adding a test substance to a cultured chondrocyte and measuring the activity for forming a chondron by using the cultured chondrocyte.” Kai *et al.* does not teach or suggest use of engineered cartilage tissue as recited in the present claims for methods that include “measuring proteoglycan loss from the engineered cartilage tissue at a time not more than 12 days from culturing, without use of a radioactive agent.” The Masuda ‘061 Patent discloses engineered cartilage tissue. However, the Masuda ‘061 Patent does not teach or suggest “measuring proteoglycan loss from engineered cartilage tissue at a time not more than 12 days from culturing, without use of a radioactive agent.”

For these reasons, reconsideration and withdrawal of the rejection is requested.

**V. Purchio *et al.* in view of the Masuda ‘061 Patent**

Claims 1-10, 14, 17-26, 33 and 35 stand rejected “under 35 U.S.C. 103(a) as being unpatentable over Purchio *et al.* (US 5,902,741) in view of Masuda.” The Applicants traverse the rejection because the combination of Purchio *et al.* and the Masuda ‘061 Patent do not teach or suggest all the limitations of the claims as amended. In particular, the combination of Purchio *et al.* and the Masuda ‘061 Patent do not teach or suggest “measuring proteoglycan loss from the engineered cartilage tissue at a time not more than 12 days from culturing, without use of a radioactive agent.”

Purchio *et al.* discloses a “three-dimensional chondrocyte culture system.” However, Purchio *et al.* does not teach or suggest use of engineered cartilage tissue as recited in the present claims for methods that include “measuring proteoglycan loss from the engineered cartilage tissue at a time not more than 12 days from culturing, without use of a radioactive agent.” Likewise, as indicated above, the Masuda ‘061 Patent does not disclose use of the engineered cartilage tissue as recited in the claims.

For these reasons, reconsideration and withdrawal of the rejection is requested.

**VI. Saito *et al.* in view of the Masuda '061 Patent**

Claims 1-8, 17-24, 29-30 and 35 stand “rejected under 35 U.S.C. 103(a) as being unpatentable over Saito *et al.* in view of the Masuda '061 Patent.” The Applicants traverse the rejection because the combination of Saito *et al.* and the Masuda '061 Patent do not teach or suggest all the limitations of the claims as amended. In particular, the combination of Saito *et al.* and the Masuda '061 Patent do not teach or suggest “measuring proteoglycan loss from the engineered cartilage tissue at a time not more than 12 days from culturing, without use of a radioactive agent.”

Saito *et al.* discloses “rabbit articular cartilage.” Saito *et al.* does not teach or suggest use of engineered cartilage tissue as recited in the present claims. Nor does Saito *et al.* teach or suggest a method that includes “measuring proteoglycan loss from engineered cartilage tissue at a time not more than 12 days from culturing, without use of a radioactive agent.” Likewise, as indicated above, the Masuda '061 Patent does not disclose use of the engineered cartilage tissue as recited in the claims.

For these reasons, reconsideration and withdrawal of the rejection is requested.

**VII. Huch *et al.* in view of the Masuda '061 Patent**

Claims 1-11, 17-27 and 29-30 stand rejected “under 35 U.S.C. 103(a) as being unpatentable over Huch *et al.* (1997) in view of the Masuda '061 Patent.” The Applicants traverse the rejection because the combination of Huch *et al.* and the Masuda '061 Patent do not teach or suggest all the limitations of the claims as amended. In particular, the combination of Huch *et al.* and the Masuda '061 Patent do not teach or suggest “measuring proteoglycan loss from the engineered cartilage tissue at a time not more than 12 days from culturing, without use of a radioactive agent.”

Huch *et al.* discloses experiments related to the use of “human articular chondrocytes in alginate beads.” Huch *et al.* does not teach or suggest use of engineered cartilage tissue as recited in the present claims. Nor does Huch *et al.* teach or suggest a method that includes “measuring proteoglycan loss from the engineered cartilage tissue at a time not more than 12 days from culturing, without use of a radioactive agent.” Rather, Huch *et al.* discloses experiments that include use of <sup>35</sup>S-sulfate as a label. As indicated above, the Masuda ‘061 Patent does not disclose use of the engineered cartilage tissue as recited in the claims.

For these reasons, reconsideration and withdrawal of the rejection is requested.

**VIII. Lansbury *et al.* in view of the Masuda ‘061 Patent**

Claims 1-8, 10, 14, 17-24, 26 and 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lansbury *et al.* (WO 94/28889) in view of the Masuda ‘061 Patent.” The Applicants traverse the rejection because the combination of Lansbury *et al.* and the Masuda ‘061 Patent do not teach or suggest all the limitations of the claims as amended. In particular, the combination of Lansbury *et al.* and the Masuda ‘061 Patent do not teach or suggest “measuring proteoglycan loss from the engineered cartilage tissue at a time not more than 12 days from culturing, without use of a radioactive agent.”

Lansbury *et al.* discloses measuring proteoglycan synthesis in a chondrocyte cell culture. Lansbury *et al.* does not teach or suggest does not teach or suggest use of engineered cartilage tissue as recited in the present claims for methods that include “measuring proteoglycan loss from the engineered cartilage tissue.” Lansbury *et al.* discloses that:

***Gross observation*** of proteoglycan-containing cartilage ECM within chondrocyte cultures may also be made. For example, chondrocytes may be stained, and proteoglycan-containing ECM material may be visualized, with a dye including, but not limited to alcian blue. (See page 25, lines 27-32, emphasis added).

However, the Applicants respectfully assert that a "gross observation of proteoglycan-containing cartilage" is not the same as "measuring proteoglycan loss from the engineered cartilage tissue." Likewise, as indicated above, the Masuda '061 Patent does not disclose use of the engineered cartilage tissue as recited in the claims.

For these reasons, reconsideration and withdrawal of the rejection is requested.

**IX. Conclusion**

In view of the foregoing amendments and remarks, it is respectfully submitted that this application is in condition for allowance.

The Examiner is invited to contact the undersigned at the number listed below if she believes such would be helpful in advancing the application to issue.

Respectfully submitted,

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